Interview July 21st, 2005, Daniel Weinberger

"It's been min-bogglingly rewarding for all of us."

THIS STRATEGY HAS HELPED US UNDERSTAND THE GENETIC MECHANISM IN PSYCHIATRIC ILLNESS

Daniel Weinberger is a Senior Investigator at NIMH and the recipient of numerous scientific awards for his research in Schizophrenia. Since 1987 he is the Chief of the Clinical Brain Disorders Branch. Research findings by his group that three genes weakly related to psychiatric disorders are strongly related to cognitive and emotional processing in brain, were classified by Science as the second biggest scientific breakthrough of the year 2003.

CW: You wrote psychiatry history and your work revolutionized the understanding of schizophrenia, and it has profound implications for our understanding of individual differences in cognition and emotion. Can you tell us how you got there?

DW: Well, I'm not sure that's where I've gotten but thank you for that very flattering statement. I got here, in some ways, without the clearest of forethought, so this was not my plan and goal to get where we currently have gotten in my program. And we've been very fortunate to have been in an environment which the intramural program the NIH has traditionally been, where one had the opportunity to follow any clue that captured one's curiosity, and that looked particularly promising, and having the independence and autonomy to pursue those clues. And that's been the intramural program and environment of the NIH traditionally; that's been the way it's been, I hope it will remain that way.

I became interested in psychiatry as a medical student in the 1970s at a time where I thought that there was a reduction in the humanism of medicine. And I became very interested in psychiatry as a more humanistic approach to sickness and trained at

Harvard in what was then a very psychoanalytic program. I was very interested in neuroscience as a medical student and I was interested intellectually in psychoanalysis, but when I got into this program I became increasingly disenchanted with the concept of being a psychoanalyst, and longed for more of the medical end of psychiatric conditions. I was very much influenced by a mentor of mine. I was the chief resident under a teacher named Richard Shader, who was a psychopharmacology expert, also happened to be a psychoanalyst, and was just a totally excellent doctor, teacher and very good clinical investigator, and had been at the NIH. I was very much under his influence and aspired to that level of inquiry that I thought he really epitomized. And I had another mentor named **Carl Salzman** who was somewhat junior to Richard Shader but was also very influential to me and was also at the NIH as a fellow. They both advised me to come here. I had two very dear friends from my residency who had come here a year ahead of me. One is Joel Kleinman who is still with me, we've done two residencies together. So I came down here with the expectation that I would learn something about research, I was interested in a career in academic medicine. And at that time, which was the late 1970s/early 1980s, this was the only way you really got that kind of training. So I came here with that expectation.

When I got here, basically, psychiatric research was primarily following biochemistry leads that were based on trying to measure a variety of chemicals. It was just in the twilight of what was the bioanalytical era of quantitative chemistry, and there were all these chemical assays. And I was very disheartened by the approach that was being taken, which was to measure chemicals in the blood and urine of patients because I felt that these were brain disorders, and if they were brain disorders you had to study the brain. And I believed the notion that trying to determine what was going on in the brain by measuring some chemical in the urine was analogous to trying to know what was happening at the back rooms of city hall by measuring constituents of the sewage system; it just didn't seem to be a very useful strategy. So I became very interested in doing studies in actual brain. And there were only two ways to do studies in brain: you could collect tissue of deceased people -- that was hard to do at that time—although my friend and colleague, Joel Kleinman, basically built his career around doing that; the other was

that there were just emerging these early efforts at having actual imaging systems that could give you pictures of the brain. And when I got to NIH, the CAT scan had just arrived on the scene.

> ***"Trying to determine what was going on in the brain by measuring some chemical in the urine was analogous to trying to know what was happening at the back rooms of City Hall by measuring constituents of the sewage system…"***

And I started in the program under Richard Wyatt, who was at the St. Elizabeth's hospital. And the NIMH had a building at St. Elizabeth's hospital, and I went to that program. I actually was never interested in coming to the main clinical center because I didn't understand how you could do psychiatric research not being in a psychiatric hospital. And so it seemed that that was the place you had to be, because that's where all the patients were. So I went to St. Elizabeth's, and that was a fantastic environment at that time in the 1980s, because it was a little bit like the French Foreign Legion, it was a complete outpost. And it had this camaraderie and outpost mentality that I thought was extremely good for thinking new things and being creative, it was not encumbered by any of the bureaucratic or traditional hierarchical problems that might limit new ideas and new ways of doing things. So I started these CT studies, and the whole idea was to look at the brains of living people. And what was clear from CT scans of schizophrenics that I was responsible for was that there were no traditional neurological findings, but it seemed to me that the story with mental illness was not going to be about brain tumors or white matter lesions or Alzheimer-like changes, it would be that brain scans would be a proxy measurement of a quantitative change in brain anatomy. So I began a series of studies to quantitatively measure brain features, and that led to the finding—which was not the first finding at all of its type, but the first from a large controlled study of young patients—that there were bigger CSF spaces, particularly ventricles in patients with schizophrenia. And we did many studies on this, not just characterizing this, but trying to understand its relationship to treatment.

I remember early on in my career I had Norman Geschwind, who had been a teacher of mine at Harvard, who was the father of behavioral neurology, come down and look at some of these patients. And he commented—he was very important—he said if this large ventricle tendency towards bigger ventricles has anything to do with schizophrenia then there should be lawful predictions that you can make about the clinical state of patients based on whether they show some of these changes or not. So we did a number of studies to do that, and it basically led to a fairly archival understanding of the fact that there were subtle but objective changes in brain anatomy that could be observed in patients. We started a series of postmortem studies and that led to a whole field which continues to grind out papers about quantitative neuroanatomy.

It was critical to develop another strategy for imaging: functional neuroimaging.

It also became clear to me early in the 1980s that, while there might be subtle anatomical changes, ultimately the illness was an illness that had its manifestations based on how the brain functioned, not on how the brain looked, but on what the brain did. CAT scan studies were not studies of how the brain worked, they were studies about how the brain looked, and that it was like a roof: the roof could be photographed, and you could see that roof had some bows in it and some bends in it, but you couldn't determine that the roof was leaking until you forced it to hold water. So I thought it was critical that we develop another strategy for imaging, which was functional neuroimaging.

And this was the early days of the PET scan, and we were beginning to do PET studies with fluorodeoxyglucose, which was a measure of glucose utilization, developed largely based on the work of Lou Sokoloff, in 2-Deoxy-Glucose. But the problem was the temporal characteristics of glucose. PET scanning was about 40 minutes, and that means you averaged brain activity over 40 minutes, which didn't seem to make any sense to me because the brain processes information at the level of microseconds, not at the level of 40 minutes. So we needed a technique that would look in a much more dynamic way to changes in the brain function. And I went to a talk in Denmark given by David

Ingvar from Sweden, where he described the method for looking at regional cerebral blood flow, which was a highly dynamic physiological measure of brain activity, and I thought this was the way to go. And back in 1983 or 1984, I convinced Fred Goodwin, who was then the intramural research program director of NIMH, to give me a half of a million dollars to purchase—no, at that time it was a hundred thousand dollars, the first systems—a hundred thousand dollars, which was a lot of money, to purchase a regional cerebral blood flow system that we housed at St. Elizabeth's hospital.

It was the only regional cerebral blood flow system of any psychiatric research program in the world, and it was the first regional cerebral blood flow system at the NIH. It was a system that was comprised—it looked like a medieval torture device, although it was completely harmless and involved no discomfort to patients. But it was a strange helmet that had 32 essentially scintillation counters applied to the subject's head. And we had them breath radioactive xenon gas, while they did cognitive tasks. I did this with a younger fellow who became my principle associate in these studies, Karen Berman, who's also still here at the NIH. My thought was that the critical issue with these kinds of studies was not to get a measure of blood flow but to use blood flow as a proxy of how the brain processed information.

And in order to do that you had to contrast blood flow patterns while the brain did a task that exercised a system in the brain that you are interested in, in comparison to when it wasn't doing that kind of an exercise. So based on discussions I had with Allan Mirsky and others here at the NIH about frontal lobe function, I picked a task called the "Wisconsin Card Sorting Task" that we had patients in normal controls do while we measured their cerebral blood flow, and we compared that to what their brains were doing while we measured their cerebral blood flow when they were doing a simple matching task. The idea was we would isolate by doing a contrast between these two conditions the brain systems that were involved in the higher order problem solving of the card sort.

I became very interested in the frontal lobes and schizophrenia. Because in 1982, I was lying on a beach in Ft. Lauderdale, and I was reading a book by Joaquim Fuster, who was a professor of neurophysiological at UCLA called "The Prefrontal Cortex." It was the first edition of that book, and I read that book, and I thought to myself, "Why has nobody ever talked to me about this." His description of aspects of frontal lobe disease malfunction, etc., had many characteristics of the cognitive and other problems associated with schizophrenia. So the early blood flow studies were designed to test specifically the hypothesis that, if we could isolate frontal processing components, we could identify a cognitively specific and system specific deficit associated with schizophrenia. And that, which was a paper published in 1986, really was the first study that documented, at the level of a mechanism, that there was a system specific physiological deficit in schizophrenia involving the frontal lobe. And that has led to probably a hundred papers by many, many groups around the world. We subsequently did a number of PET studies on that, we've done a lot of imaging studies on that using functional magnetic resonance imaging, EEG studies, many, many different, more refined, more sophisticated studies than our early blood flow techniques, but basically confirming with much more sophisticated methodology and much more complex signal processing mathematics the basic discovery of a physiological dysfunction of this dorsolateral prefrontal cortex in schizophrenia.

In 1993, I made everybody in the lab come with me to take a ten-day course in recombinant DNA technology.

Those were the many areas that we studied for probably 15 years until the early 1990s when I attended a meeting of *The National Academy of Sciences* where Harold Varmus was there, and this was in the early days of the human genome project when it was just starting. I became very convinced that the *Human Genome Project* was going to succeed, and that we would have genes for mental illness. And I said to myself, "Once we have these genes, we're going to have to understand them because whether we like genes or not, they will represent the only absolutely objective clues to the basic causes of the illness." Everything that we had done up to that point for basically 12 years of my

career, everything that we had done was based on characterizing the phenomenology of the illness. Even though the phenomenology would be very elaborate, sophisticated and cool at the level of brain physiology and brain anatomy, it was all phenomenology. We were contrasting people who were ill with people who weren't ill. Genes were not phenomenology; genes were basic mechanisms of disease. So I became very concerned that we would not be ready for these genes.

And, actually, we were just talking about this at lunch today, in 1993 I made everybody in the lab come with me to Catholic University to take a ten-day course in recombinant DNA technology in the laboratory. We began to retool the entire program around genetics and molecular biology. And then in the early 1990s, about 1993, I started working with Joe Frank down here in the FMRI unit, when the early days of functional magnetic residence imaging began, and when we first started doing these studies that involved no radioactivity but had higher both spatial and temporal resolution than PET, it dawned on me that since there was no radioactivity, and we could study the same subject repeatedly as their own control, we could actually do phenotyping at the level of brain function in individual subjects. And once you had individual subjects, you had a phenotype that you could relate to a gene. It always seemed reasonable to me that schizophrenia was not really about schizophrenia, it was about brain processes that led to the emergence of this clinical condition. The clinical condition was likely to be a real secondary phenomenon related to more basic brain processes, which ultimately had genetic origins. So I became very excited about the idea that there was a strategy now for imaging with high temporal and spatial resolution that could be used as a target phenotype to understand gene effects in the brain.

People looked at me like I had lost it completely…

One of the things that have characterized my whole career, by the way, has been presenting ideas for novel strategies to understand psychiatric illness that caused me to be laughed out of the room of the people I've told this to. So when I first started doing CAT scan studies, I went to Giovanni Di Chiro, who was then head of radiology at NIH, and I

said, "You know, I think we have bigger ventricles in these patients, what do you think about this?" And he completely kicked me out of his office, thought it was a completly meaningless observation, had no relevance. When we wanted to first do blood flow studies and I tried to convince the department here to think about doing PET regional cerebral blood flow rather than glucose, they thought it was ridiculous; that it would have no value because it would be too transient. And then, when I went to the radiology people with the idea that maybe we can use functional magnetic resonance imaging to do genetics in the brain people looked at me like I had lost it completely. Well, the fact of the matter is, because the NIH has made it possible for people to pursue ideas that at their face may look a little bit extreme, these things have turned out to be very valuable strategies.

When I first started our genetic study, where we were focused on genes about brain development, brain functioning, temperament cognition, and not genes from mental illness, I went to the Genome Institute, and talked to the then scientific director at the genome institute, and I said, "We think that we can define intermediate phenotypes. Not clinical phenotypes, but aspects of brain function based on imaging and cognition that will show greater gene effects than the clinical diagnosis. We want your help with this." They literally kicked us out of the office. They thought it was the most preposterous thing they ever heard, because it was very different from their traditional Mendelian linkage-based strategies. They said, "Bring us high-density families, we'll find you genes." That strategy has not found genes, and this strategy has helped us understand the genetic mechanism in psychiatric illness. So it's basically evolved over the last ten years.

We have discovered not just genes for schizophrenia, but we have been able to begin to explore what those genes do in the brain that accounts for why they translate into psychiatric illness.

We changed the program dramatically beginning in about 1995. We were still at St. Elizabeth's; we moved here in 1998 to reorganize everything that we did—imaging, patient assessment, cognition—around trying to characterize phenotypes that would be

related to the genetic origins of the disease. And we began to organize a study, which we called the Sibling Study, the Clinical Brain Disorders Branch (CBDB) NIMH Sibling Study, where we collected families that had an affected offspring and an unaffected sibling and two parents. All we got from the parents was the DNA, we got DNA from the siblings, and we put them through a two-day study here at the NIH involving imaging, cognition, EEG, many, many personality and other kinds of inventories, and we have also acquired normal controls at the same time. Over the last nine years that we have been doing this study, we have studied over 1,500 people. We have imaging cognitive data sets, temperamental inventories of over 500 normal people, over 500 patients with schizophrenia, over 500 of their healthy siblings; and we have human cell lines on over 1,500 of these people, we have DNA from about 800 of their parents. So it has become a phenomenally rich archival data set to look at how genes affect aspects of human brain function related to psychiatric illness, related to temperament, etc. And I think where all this has led now is that we have discovered not just genes for schizophrenia—which many groups have discovered, we have now probably 10 to 15 schizophrenia genes—but we have been able to begin to explore what those genes do in the brain that accounts for why they translate into psychiatric illness. And this has emerged from the application of cognitive analysis, imaging studies, in addition to postmortem brain, gene, and protein expression studies to the genetic variations that are associated with mental illness. And that's where the work is right now. That is the story.

CW: That's great. So you say, when did you start to collect this database?

DW: It began about 1996.

CW: And when you conceived of the phenotyping studies, you conceived of it first, searching for schizophrenia genes, or you thought immediately of normal people?

DW: We always thought that the issue was not schizophrenia genes. I mean, the genes are not about hallucinations and illusions. Genes are about molecular processing and cells. And we always assumed that, just as an intermediate phenotype for colon

cancer is a colon polyp, the genes had to be about how your brain developed and how it worked. And that ultimately, the psychosis and the other problems were downstream manifestations of these more proximate biological phenomena. And it was, to me, very obvious that the closer you got to the biology of the gene, the more strong the gene effects would be, and the biology of the gene related to mental illness is the biology of brain, and that if we could study genes in the brain, we would see much more robust effects. And now ultimately, the studies in normals are because the variations in the genes are compensated for in normals, or normals don't have additional factors that interact with the set of susceptibility genes. But they also don't have confounding factors like alcoholism, drugs, etc., so you could see pure effects of the genes in the normals. And we have consistently shown now that by using brain phenotyping, not clinical illness but brain phenotyping, that the genes related to clinical illness in people, who are clinically ill, translate into lawful, predictable variations in how critical systems in the brain related to cognition and emotion process relevant kinds of environmental stimuli. I tried to cover a lot of your questions.

CW: Yes, you covered everything. [laughs] But I would like to ask, the clinical brain disorders branch was created in 1987…?

DW: Right.

CW: So that was at St. Elizabeth's, and then you moved here in 1998. Why did you move here?

DW: We moved here because the NIMH was having—we moved here primarily to save money. The building at St. Elizabeth's had begun in like the mid-'50s, and was started by Seymour Kety, who was the scientific director of NIH. And it was based on the idea that the Mental Health Institute should have a research center at a mental hospital, and St. Elizabeth's was a federal neuropsychiatric hospital. We had a great building there, about 250,000 square ft. It was old, 1950, but it was a great building, with great labs. And as I said, we were like the French foreign legion: we operated completely

autonomously. We had our own crew, staff, we had our own building crew. If we had to get an office renovated, we did it ourselves. If we had to build a lab, you know, everything -- you know, Floyd Bloom had been there; it was a great environment. We had our own monkey program; we had about 50 rhesus monkeys there, We had terrific animal facilities.

Anyway, but by the mid 1990s, the landscape had changed. What had been a very rich neuroscience community where there were always four or five labs there had become really two labs: my own lab and Richard Wyatt's lab. We were losing the critical mass of scientists that we needed to have there, because it became increasingly hard to get people to go there. In the 1970s and 1980s, everybody wanted to go there because it was such a great place to work. But as things at the main campus moved much more into molecular neuroscience, it became more isolated. Really by the mid-1990s it was clear that its heyday was passed. And then because that building that we occupied cost about $4 million a year in rent to St. Elizabeth's, the contractions in the program, it really made sense to just bring it back to the main campus. And this has definitely been the right place to do this kind of work.

CW: And there is the "Unit for Systems Neuroscience in Psychiatry," when was that created?

DW: I'm not sure what that is, actually.

CW: Well I found that on your website, that's part of the Clinical Disorders Branch.

[laughter]

DW: Okay, well we have a number of units in the program. The program has changed. It was a basic lab until two years ago, and the lab has two sections, the clinical research section and a post-mortem study section, and within each section there are

multiple units that are really groups of investigators based on different strategies for doing these investigations. So the unit for systems neuroscience, do you know who heads that unit?

CW: Andreas Meyer-Lindenberg.

DW: Oh, Meyer-Lindenberg. Okay, that's a very new unit. That's a new unit based on one of our newest tenure track investigators. We just formed that unit this year based on Andreas Myer-Lindenberg becoming a tenure track investigator, he is a neuroimaging investigator who has a much broader vision about applications of neuroimaging than the traditional vision. And he is one of the really talented, young signal processing imaging investigators who is using genetics, systems neuroscience, and complex strategies for functional imaging analysis to explore novel ways of using imaging to understand systems, neurosystem function and ultimately genetics in the brain.

CW: I see, I was wondering, because, then there is the "Genes, Cognition, and Psychosis Program" that was created in 2003, but that would also address systems…?

DW: Yes, well there are many different -- everybody is investigating systems. The *Genes, Cognition, and Psychosis Program*, which began two years ago, was an effort to capitalize—this was largely because of Tom Insel's, I think, support and really active interest in the work that we have done. For the first time ever in my entire career at NIMH, we have had an institute director who is trying to enhance our efforts and not to frustrate our efforts. I've never had an institute director, previously, who has tried to help us. And Tom was the first institute director who was not threatened by the work that we did. So Tom was very, very eager to encourage us to pursue this work. And he recognized immediately that these genetic insights were of enormous importance. So we realized that we could no longer keep this work in a lab but we needed to bring in investigators with expertise across the NIH community. And the idea of the program was that we now had resources to recruit investigators in other institutes.

There are four Institutes now involved in the program. So we are funding investigators in the Cancer Institute (NCI), in Child Health and Human Development (NICHD), in Neurology (NINDS), and in NIMH. So the program is across Institutes, it's based on engaging investigators who have expertise or skills that are not in NIMH and have all of these people work with the same vision, which is to understand the mechanisms of genetic susceptibility to mental illness, but to use a variety of different strategies: imaging, cell biology, animals, basic molecular genetics, stem cells, to try to understand these mechanisms. That's what the *Genes, Cognition, and Psychosis Program* is now. It engages four different laboratories in four different institutes in various ways in trying to map, at the cellular and brain level, the mechanisms by which these genes operate.

CW: Yes, if one looks at the papers that came out in the last few years, it really seems as if it's a strategic effort, to do all of these studies, they are coordinated, and then also the way that papers are published, it's really like building a solid…

[laughter]

DW: Well, it's been mind-bogglingly rewarding to all of us. The other thing is, I think we have managed—this was partly from our history at St. Elizabeth's, when you're in the French Foreign Legion so to speak, or you're in an out post like this, there's a tremendous amount of collegiality and camaraderie, and St. Elizabeth's program was famous for this, which was not what people often said about the intramural program at NIH. We were famous for having a certain *esprit de corps* and that's probably because we were a little bit isolated and we all had to work together. And so one of the things that I think has characterized the program here is that we have been a very well-functioning, long-together team of people working together, sharing many aspects of this work—both the credit, the details, the sweat, and it's been a very rewarding effort, I think, on many levels. We have brought many people into the genetics of this from areas outside of genetics; we very strongly encouraged people to get much more familiar with the genetics, much more sophisticated with the genetics; we brought people into imaging that would never of thought of setting foot anywhere near imaging data, because we have

tried to treat all of these approaches as tools to characterize the biological mechanisms involved. And so I think part of the real reward of this whole thing has been this team of people.

It's been mind-bogglingly rewarding to all of us

We have had, you know, a group of us now that have been together for 15 years working on this. The main pillars of this group have been together 15 years. We are actually at a very significant milestone because two of our principal pillars, Michael Egan and Terry Goldberg, are both leaving. And they're leaving literally this month. And those people have been with me since the mid-'80s, almost 20 years—Terry's been with me 20 years, Michael about 18 years. And they have been absolute pillars of the community, among my most valued scientific collaborators. But you know, nothing lasts forever.

CW: Where are they going?

DW: Michael Egan is going to Merck Pharmaceuticals, and Terry Goldberg is going to Albert Einstein Medical School in New York. Both accepting very significant positions, as they should have.

CW: So how big is the group?

DW: Well, the group has many different incarnations. The Genes, Cognition, and Psychosis Program, which involves many independent groups of investigators, I think probably is a hundred people overall, you know, but there are all these different labs, they are linked by virtue of some of their common projects. The clinical brain disorders is sort of a branch itself. In terms of the number of investigators, maybe there are 10 or 15 investigators, but there are a lot of other students, and we have what is a very nurturing environment, which I think is part of why we all feel kind of invigorated by it because it's very multi-dimensional.

CW: I was wondering when I looked at the papers, on the one hand, scientifically it is just fascinating and stunning, and on the other hand I was wondering what can be done with the results? Do you think about that, or do you control what's happening to your results? Because there is this issue of normativity that the studies raise. When they talk about the COMT val/met alleles for instance, the way it's put in the paper is often as if the met/met version was the standard, or the norm.

DW: Well, we have some papers coming out on that. This is a very evolving area of work, because we are really scratching the surface of understanding human temperamental variation, cognitive variation, psychiatric variation. And as we get deeper and deeper into these genes, we begin to appreciate more and more that they are all about the flavorings of human variation. So while Met/Met's may have a much more efficient way of dealing with cognitive information, they actually have a much less efficient way of dealing with emotional information. There are yin-yangs to these things, no gene is about only one thing. And that's partly why there's a lot of Val/Val and a lot of Met/Met's around. Because there are advantages and disadvantages to each form of the gene, based on what the specific environmental context is. And this is very complicated human biology of normal variation because these genes have been interacting with the environment, changes in the environment and other genes, for millions of years. And so a lot has happened to balance off different functional changes in these genes, and I think the environmental context of change, and they select for different properties. It is a very infinitely complex but very fascinating story.

It took about 40 years, 45 years to find out what it had to do with mental illness, because it was not really about the way it had been studied, it was about the frontal cortex and genetic variation.

One of the reasons we have put a lot of energy into COMT is because it has this functional variation that we can study by asking lawful questions. We understand a lot about the biology. COMT, the enzyme Catechol-O-methyl transferase, was discovered by

Julius Axelrod. And before he died, I had lunch with him probably monthly for a period of time, because we were obviously very taken and enthusiastic, and really quite taken by this whole COMT phenomenon. And he was ecstatic that this protein he had identified as an enzyme had a whole new life and was being understood at a level that they had never had the tools to study it at. And this was his favorite molecule, he won the Nobel Prize for catechol-O-methyl transferase. It's fascinating that Seymour Kety, who was then the scientific director of NIMH, when Julie Axelrod found COMT, said, "If this enzyme, this protein, has nothing to do with mental illness, no protein does." It took about 40 years, 45 years to find out what it had to do with mental illness, because it was not really about the way it had been studied, it was about the frontal cortex and genetic variation. But that's the old story, that progress is new solutions to old problems.

CW: So there is serendipity that at the moment when you were working, molecular biology and brain imaging technologies were both available.

DW: Yes, definitely, absolutely. Well you know, there's always that, [laughs] Julie Axelrod said this, he said, "Being a good scientist is not about brilliance, it's about asking the right question at the right time." It's about perseverance, asking the right question at the right time. I personally don't think any of these questions are brilliant, it's just a matter of where your head is, and how you see what question interests you, and being doggedly persistent, because we've been just hammering away at this concept that mental illness is about brain function, not about behavior, and that what are the best tools to get at that imaging clearly was the best tool to study brain function.

I like to say the basic science of psychiatry is neuroscience and genetics, that's it. And the only in vivo tools for neuroscience are imaging. I mean, in some ways it's simple, it's like, these are all we've got. And you've got to say to yourself, what are the best questions you can ask with the tools that are the best tools you have? And that's what I think it's been a little bit about. I always remember that this famous sculpture of Picasso's, called "The Bull's Head," which was a bicycle seat like this and a set of handlebars, and you look at this thing and you go, "Why is this a great piece of art?

Anybody can take a set of handlebars and put them on top of a bicycle seat." Well the answer is, Picasso saw a bull's head in a bicycle seat and a set of handlebars. And I think the reality here is that there's no real magic in any of this. It is just about trying to shape the question based on a skeptical, critical view of what is the dogma—which has always been the way I've approached this stuff—and trying to optimize the tools that are out there to ask those questions. And I think we've been lucky to be in a position to be able to do so. I've also been extremely lucky to be in an environment where there's all these talented people to work with, who've been willing to buy into this vision which many people didn't think would go anyplace. Our previous NIMH director thought that this was a complete waste of time and was very, very negative about it, and did everything he could to thwart it. We all know who that was.

CW: [laughs] So it must be especially gratifying to have this research classified as one of the most important "scientific breakthrough's of the year" in *Science* 2003?

DW: Oh yeah, that was very gratifying. That was gratifying. I mean, I don't know if it's gratifying, I mean, to be honest, it's flattering. What is gratifying, really, is that we have real genes and real mechanisms by which the genes work. And what is really gratifying is to feel that we are no longer elaborating phenomenology but dealing with basic mechanisms of causation and that, I believe, that some of these findings are truly meaningful at the basic level of causation. And that is gratifying. The *Science* thing was flattering, and it was a relief, because it meant that we would have a honeymoon for a period of time to continue to do this before the next person who found it threatening or difficult would come after us and try to limit it. [laughter] So to that extent we have a reprieve now for a little time, we have a honeymoon for a little while to keep hammering away at this.

CW: Well, great. Thank you very much.

DW: So you've got the science and the politics in one place.